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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/696,909 | 10/29/2003 | James B. Lorens | 7946-79836-01 | 9257 |

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| EXAMINER | |
|---|---|
| REDDIG, PETER J | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 01/27/2011 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| **Advisory Action Before the Filing of an Appeal Brief** | **Application No.** 10/696,909 | **Applicant(s)** LORENS ET AL. | |
|---|---|---|---|
| | **Examiner** PETER J. REDDIG | **Art Unit** 1642 | |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 03 January 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *03 January 2011*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,14-18,27,41-44,54 and 55*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Peter J Reddig/
Primary Examiner, Art Unit 1642

Continuation of 11. does NOT place the application in condition for allowance because: Claims 1, 14-18, 27, 41-44, 54 and 55 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mor, O. (US Pat. App. Pub. 2003/0157573 A1 Feb. 12, 2002) in view of Klinghoffer et al. (United States Patent Application Publication No.: 2004/0077574, May 23, 2002, previously cited), further in view of O'Donnell et al. (Am. J. Path. 1999, 154: 1171-1180, IDS item), and, further in view of Varner and Cheresh (Current Opinion in Cell Biology, October 1996, 8:724-730, previously cited) for the reasons of record.

Applicants argue that the analysis for determining obviousness under 35 U.S.C. § 103(a), as articulated in Graham v. John Deere Co. 383 U.S. 1 (1966), requires 1) determining the scope and content of the prior art; 2) ascertaining the differences between the prior art and the claims at issue; and 3) resolving the level of ordinary skill in the pertinent art. Graham, 383 U.S. at 7. In particular, ascertaining the differences between the prior art and the claims requires that both the claims and the prior art be read as a whole (M.P.E.P. § 2141.02; In re Langer, 465 F.2d 896, 899, 175 USPQ 169, 171 (CCPA 1972); W.L. Gore &Associates v. Garlock, Inc., 721 F.2d 1540, 1551, 220 USPQ 303,311 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984)). "All of the disclosures in a reference must be evaluated for what they fairly teach one of ordinary skill in the art... [W]hen 'all of the disclosures in a reference' are considered, the overall suggestion to emerge from the prior art reference may be contrary to that which might appear from an isolated portion of the reference." In re Langer, 465 F. 2d at 899, 175 USPQ at 171.

Applicants argue that the Office asserts that it would have been primafacie obvious to combine the teachings of Mor and Klinghoffer et al. to use RNAi molecules in the screening methods of Mor to identify effective anti-angiogenic drugs (Office action, page 4, first full paragraph). The Office states that one of skill in the art would have been motivated to combine these references in order to identify the most effective angiogenesis inhibitor and would have had a reasonable expectation of success (Office action, page 4, first full paragraph).

Applicants argue that the combination of Mor and Klinghoffer et al. does not include all of the limitations of the pending claims. The Office acknowledges that Mor does not disclose a method that includes assaying alpha V beta 3 expression, tube formation, or haptotaxis (Office action, page 3, third full paragraph). Klinghoffer et al. disclose siRNAs and their use as therapeutics for a range of diseases, but likewise does not disclose methods that include assaying alpha V beta 3 expression, tube formation, or haptotaxis. Thus, the combined references do not disclose all the limitations of Applicants' claims, and the Office has not set forth a reason that one of ordinary skill in the art would have modified these references to arrive at Applicants' claims. Therefore, the Office has not established a primafacie case of obviousness.

Applicants argue that furthermore, Mor is focused on identifying inhibitors of Axl for use in treating fibrosis (particularly renal fibrosis) and glomerulosclerosis (Mor, paragraphs [0033] and [0036]). These conditions are characterized by proliferation of fibroblasts, overproduction of connective tissue proteins and thickening of the basal membrane of the glomeruli (Mor, paragraph [0007]). In addition, Mor indicates that appropriate cell-based assays for measuring Axl activity include cell survival, cellular differentiation, and cell proliferation (Mor, paragraph [0059]). Mor states that compounds identified in its screen may be useful for treating nephropathy, kidney fibrosis and other fibrotic diseases, and restenosis, which is a proliferation of smooth muscle cells (Mor, paragraph [0090]). Finally, Mor states that the compounds "may also be used as anti-angiogenic drugs for the treatment of cancer and other conditions where preventing or reducing proliferation of endothelial cells is desired" (Mor, paragraph [0090], emphasis added). Taken as a whole (as required by the M.P.E.P and case law, as cited above), Mor discloses an assay for identifying inhibitors of Axl utilizing cell proliferation as the indicator of Axl activity, rather than an assay for identifying inhibitors of angiogenesis, as recited in Applicants' claims. Klinghoffer et al. discloses Axl only as containing a potential PTP1B domain (paragraph [0016]), and does not suggest any role of Axl in angiogenesis.

Applicants argue that one of skill in the art might have been motivated utilize the methods disclosed in Mor and Klinghoffer et al. to identify an siRNA inhibitor of Axl which inhibits cell proliferation with a reasonable expectation of success. However, the disclosure by Mor that an inhibitor of Axl could be identified by assaying cell proliferation, even proliferation of endothelial cells, does not make it predictable that a compound identified by such a method would inhibit an angiogenesis phenotype such as alpha V beta 3 expression, tube formation, or haptotaxis in endothelial cells expressing Axl (despite the use of the term "anti-angiogenic" by Mor in paragraph [0090]). Thus, one of skill in the art would not have been motivated to modify the methods disclosed in Mor to assay alpha V beta 3 expression, tube formation, or haptotaxis in combination with Klinghoffer et al. to identify an inhibitor of angiogenesis, particularly when Mor is considered as a whole. Therefore, Applicants' claims are not obvious over the combination of Mor and Klinghoffer et al. and withdrawal of this rejection is requested.

Applicants' arguments have been considered, but have not been found persuasive because the combination of Mor and Klinghoffer et al. were not solely relied upon to reject the claims. Thus, although Mor and Klinghoffer do not disclose alpha V beta 3 expression, tube formation, or haptotaxis, the rejection was not solely based on these references and, thus, Applicants' arguments are not found persuasive.

Applicants argue that the Office also asserts that it would have been primafacie obvious to combine the teachings of Mor, O'Donnell et al., and Varner and Cheresh to measure alpha V beta 3 expression or tube formation in endothelial cells because "Mor teaches assaying cellular differentiation .... O'Donnell et al. teaches that Axl may be involved in tube formation during angiogenesis, and Varner and Cheresh teach that alpha V beta 3 expression is [a] critical event of blood vessel formation..." (Office action, page 4, second full paragraph). The Office also asserts that Varner and Cheresh disclose that alpha V beta 3 is important [in] endothelial cell survival (like Axl), and inhibition of alpha V beta 3 inhibits angiogenesis" (Office action, page 4, second full paragraph).

Applicants again emphasize that Mor, when read as a whole, teaches methods of identifying inhibitors of Axl by assaying cell proliferation, cell survival, or cellular differentiation in fibroblast or mesangial cells (e.g., paragraph [0059], claims 5-9). Based on Mor, one of skill in the

art would not have been motivated to utilize an assay measuring alpha V beta 3 expression, tube formation, or haptotaxis in an endothelial cell expressing Axl to identify an angiogenesis inhibitor. O'Donnell et al. describe the expression of Axl in capillary endothelial cells (page 1174, left column) and the role of the Axl ligand Gas6 in increasing endothelial cell survival and/or decreasing endothelial cell apoptosis (page 1175-1176). This is acknowledged by the Office, which states "O'Donnell clearly shows that Axl is expressed in endothelial cells and is involved in their viability and survival" (Office action, page 6, second full paragraph, emphasis added). O'Donnell et al. speculate that Axl may be involved in cell adhesion, and could therefore be "relevant to tube formation in angiogenesis" (page 1176, fight column) and note that Gas6 can elicit chemotaxis of vascular smooth muscle cells (page 1177). However, O'Donnell et al. also note that Gas6 is a "promiscuous ligand" for the Axl subfamily (which includes Axl, Sky, and Mer tyrosine kinases) and that "Gas6 has been shown to protect a number of Axl-positive cells from stimuli that induce apoptosis" (page 1178, fight column). Other effects of Gas6 (such as chemotaxis) may be due to the "promiscuous" effects of Gas6 and not specific to Axl.

Applicants argue that based on the focus of Mor on Axl inhibitors as potential inhibitors of cell proliferation and that of O'Donnell et al. on Axl as a mediator of cell survival, one of skill in the art would not have been prompted to assay markers of angiogenesis such as alpha V beta 3 expression, tube formation, or haptotaxis in endothelial cells. In particular, the disclosure of O'Donnell et al. is highly similar to that of Healy et al. (Am. J. Physiol. Lung Cell Metabol. 280:L1273-L1281, 2001), which was previously cited by the Office in a rejection under 35 U.S.C. § 103(a) in combination with Varner and Cheresh and Klinghoffer et al. (e.g., Office action dated June 23, 2008). That rejection was overturned by the Decision of the Board of Patent Appeals and Interferences (Appeal 2009-011194, March 16, 2010), which stated that "Healy' s investigation focused on determining the role Gas6 plays in endothelial cell survival and in Axl-related apoptotic cell death...The Examiner has not adequately explained why an ordinary artisan studying the effects of Gas6 HPAEC on Axl-mediated apoptosis of HPAECs, as taught by Healy, would have been prompted to assay the expression of alpha V beta 3, an angiogenesis marker, in those cells" (Decision, page 17, last paragraph). Furthermore, one of skill in the art would not have had a reasonable expectation of success that a method including assaying alpha V beta 3 expression, tube formation, or haptotaxis in endothelial cells expressing Axl would identify an inhibitor of angiogenesis based on the speculative statements included in O'Donnell et al. regarding a potential role of Axl in vascular structure and function.

Applicants argue that finally, Varner and Cheresh describe the role of alpha V beta 3 integrin in the process of angiogenesis (page 726, right column) and disclose that an alpha V beta 2antagonist inhibits angiogenesis (page 726-727). However, this reference does not teach or suggest a role for Axl polypeptide in angiogenesis. Therefore, the combination of Varner and Cheresh with Mor and O'Donnell et al. does not provide a motivation for one of skill in the art to measure alpha V beta 3 expression in the assay of Mor (which as discussed above, is directed to cell proliferation), nor provide a reasonable expectation of success. Therefore, Applicants' claims are not obvious over the combination of Mor, O'Donnell et al., and Vamer and Cheresh, and withdrawal of this rejection is requested.

Applicant's arguments have been considered, but have not been found persuasive. Mor teaches, as previously set forth, methods of identifying Ax1 receptor kinase inhbitors, including assaying cell differention in endothelial cells, to identify these inhibitors, and teaches that these inhibitors can be used to inhibit angiogensis. Thus, one of skill in the art would have been motivated to examine the effects of these potential inhibitors/antagonists on markers and functions of angiogenesis. Given that O'Donell teaches that Axl is expressed in endothelial cells and that it is important for their survival and potentially in tube formation and Varner and Cheresh teach that alpha V beta 3 is critically involved in angiogenesis, one would have been motivated to examine these hallmarks of angiogeneis in the screening methods of Mor et al. With regard to the previous Decision of the Board of Patent Appeals and Interferences the instant rejection is not based upon Healy, thus the arguments are not probative on the instant rejection. Thus the rejection is maintained for the reasons of record.